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# CDX2 immunohistochemical expression in human colorectal adenocarcinoma and gastric adenocarcinoma: A comparative study

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**Abstract**
**Background:** Caudal-related home box gene two (CDX2) is home box domain containing transcription factor that is important in the development and differentiation of the intestine. Aim of the study: to examine the expression of Caudal-related home box gene two in a series of colorectal and gastric adeno carcinomas, and correlate its expression with different clinic pathological parameters including: tumor type grade stage and compare its expression between the two malignancies.
**Material and Method:** this is a retrospective study of a total of fifty cases including twenty five cases of colorectal carcinomas and twenty five cases of gastric adenocarcinoma were collected from the histopathology laboratory department of gastroenterology and hepatology teaching in Baghdad (from January 2021 to January 2022); slides were prepared from paraffin blocks and stained with Hematoxylin and Eosin for histopathological revision and others were stained immunohistochemically with CDX2, CDX2 expression was semi-quantitatively scored. Correlation between clinic pathological parameters and CDX2 expression was done.
**Results:** Regarding the twenty-five cases of colorectal adenocarcinoma: age range was (45-85) years,15 (60%) of cases were males, 10 (40%) of them were females, most common cases 23 (92%) were grade 2, and most common 18 (72%) of the cases were stage T3, most common cases 16 (64%) cases had no lymph node involvement (N0), all the cases showed positivity for or CDX2,17 (68%) of cases had CDX2 score (3) while 8 (32%) of them had CDX2 score (2). Regarding the twenty five cases of gastric adenocarcinoma: age range was (24-69) years,17 (68%) of were males, 8 (32%) of them were females, most common 14 (56%) of the cases were grade (2), and most common stage 20 (80%) of the cases were stage T3,most common cases 7 (28%) had no lymph node involvement (N0), most 15 (60%) of the cases showed positivity for or CDX2, 9 (36%) of cases had CDX2 score (1), 5 (20%) of cases showed score (2),1 (4%) of cases showed score (3), while 10 (40%) of the cases were negative for CDX2 (score 0).
**Conclusion:** CDX2 marker is already proven as highly sensitive in colorectal adenocarcinoma. There was a significant correlation between CDX2 score and the site of the tumor (colorectal versus gastric).

**Keywords:** CDX2, adenocarcinoma

## Introduction
Gastric adenocarcinoma is the fourth most common malignancy in the world and is still the second leading cause of cancer mortality in the world [1]. Helicobacter pylori infection, atrophic gastritis, intestinal metaplasia, and dysplasia are patho-etiologically related to gastric adenocarcinoma [2]. Surgical resection is the mainstay of treatment and can cure patients with early-stage cancer. The survival rate of patients with advanced respectable gastric or gastroesophageal junction (GEJ) cancers, however, remains poor despite new treatment strategies, such as perioperative chemotherapy [3] or adjuvant chemo radiation. In Western countries, most gastric cancer patients are diagnosed when the tumor is at an unrespectable stage. For these patients, systemic chemotherapy is the main treatment option, because it prolongs survival without comprising the quality of life [4]. Microscopic types including diffuse, intestinal, mucinous, papillary, tubular, mixed, and Adeno-squamous carcinoma among others [5]. Colonic carcinoma is the most common malignancy of the gastrointestinal system and is one of the main causes of mortality and morbidity worldwide [6].

According to the Iraqi cancer registry data 2019 colorectal cancer was one of the top ten cancers in both genders, in male patients it ranked third after (bronchus and lung) and urinary bladder (8.02%), in female patients it was fourth after breast, thyroid gland, brain and other central nervous system tumors (CNS) [7]. Colon cancer has ranked 2nd after breast cancer with total number of 865, 630 new cases in females, 3rd after lung and prostate cancer in males with 1,065,960 new cases, worldwide, of all ages. In Iraq it was the third most common cancer and accounted for 797 deaths out of 1,305 new cases and 5.4% mortality rate [8]. The most common symptom reported was fresh bleeding per rectum while the least common symptom was weight loss [7]. The development of colorectal is multifactorial, and risk factors include various lifestyle, genetic, and environmental factors. It has been estimated that at least half of colorectal cases could be prevented by a reduction in known modifiable lifestyle related risk factors [7]. The CDX2 protein: (caudal-related home box transcription factor 2), is expressed in the nuclei of intestinal epithelial cells. Its function is related to Wnt-signalling, homeostasis and permeability. it is a relatively specific marker for colorectal carcinoma, with a 70 to 100% expression incidence in tumor cells compared with normal cells, However, the CDX2 can also be expressed in other primary-stage mucin producing carcinomas such as bladder, ovarian, lung, sinonasal intestinal adenocarcinoma, pancreas, and biliary carcinomas [9]. Aim of study to examine the expression of Caudal-related homeobox gene two in a series of colorectal and gastric adeno carcinomas, and correlate its expression with different clinic pathological parameters including: tumor type grade stage. and compare its expression between the two malignancies.

## Method

This is a retrospective study including formalin fixed, paraffin embedded tissue blocks for cases diagnosed histopathologically as gastric and colorectal adenocarcinoma, collected from archived materials from Gastroenterology and hepatology teaching hospital, Teaching laboratory institute and some private labs. in Baghdad (from January 2021 to January 2022). Fifty formalin fixed, paraffin embedded tissue blocks of gastric and colorectal adenocarcinoma Cases were included in this study, 25 cases were gastrectomy (total, subtotal) and 25 were colectomy (hemi colectomy, total colectomy, AP resection). Regarding gastric cases 9 were diffuse while 14 were intestinal type adenocarcinoma. Age of patients range from 24 years to 85 years and it was divided into (21-30, 3140, 41-50, 51-60 and >60) year. The clinicopathological parameters studied including: age gender, tumor grade and stage were obtained from archive materials. Two sections of 5µm thickness were taken from each block, the first was stained with hematoxylin and eosin stain (H and E) for histopathological revision, the other section was stained immunohistochemically for CDX2 expression, the working was done in the teaching laboratory institute on February 2022. Inclusion criteria for cases collection: Cases with different grades and stages (for both gastric and colorectal carcinoma). Available clinical data and material blocks.

Exclusion criteria for cases collection: Incomplete clinical data. Endoscopic biopsies were excluded

To consider CDX2 as positive stain, a dark brown nuclear stain of the malignant cell should be found and this is done at X40 objective. CDX2 immunohistochemical marker in the study was scored as follows: • 0 (no positivity or only very occasional cell staining), 1+ (<10% of cells stained), 2+ (10-50% of cells stained), 3+ (>50% of cells stained). The intensity of staining was also scored on a categorical scale from 0 to 3: 0 indicated absent; 1+ very weak, dubious staining; 2+ definite, mild, or moderate staining; 3+ definite, strong staining. Only tumor cells stained in the appropriate nuclear location were scored [10]. Positive control: Colonic tissue, as mentioned in the leaflet [11]. Statistical package for social sciences version 24 (SPSS v24) used to analyze data. Continuous variables presented as means with standard deviation and discrete variables presented as numbers and percentages. Chi-square test for independence and Fisher's exact tests were used as appropriate to test the significance of association between discrete variables. Level of significance was set at P value < 0.05.

## Results

### A. Colorectal carcinoma

25 Patients with colorectal Ca., mean age of patients (63.4 ± 12.76) years old. With Min (45) and Max. (85) years old. Mean size of tumor (5.39 ± 2.56) mm. 15 (60%) of patients are males and 10 (40%) are females, 18 (72%) of patients are at stage 3 of illness, 23 (92%) of patients are at grade 2 of illness, 16 (64%) of patients 0 involvement of lymph node. As show in table 1.

**Table 1:** Distribution of variables in current study.

| Variables | | frequency | percentage |
|---|---|---|---|
| Gender | Female | 10 | 40.0 |
| | Male | 15 | 60.0 |
| Stage | 2 | 5 | 20.0 |
| | 3 | 18 | 72.0 |
| | 4 | 2 | 8.0 |
| Grade | 1 | 1 | 4.0 |
| | 2 | 23 | 92.0 |
| | 3 | 1 | 4.0 |
| Lymph node | 0 | 16 | 64.0 |
| | 1 | 4 | 16.0 |
| | 2 | 5 | 20.0 |

According to fig (1, 2); 17 (68%) of patients have CDX2 score 2, 8 (32%) of them have CDX2 score 2. 13 (52%) of patients at age group >60 years while 7 (28%) of patients at age group 51-60 years.

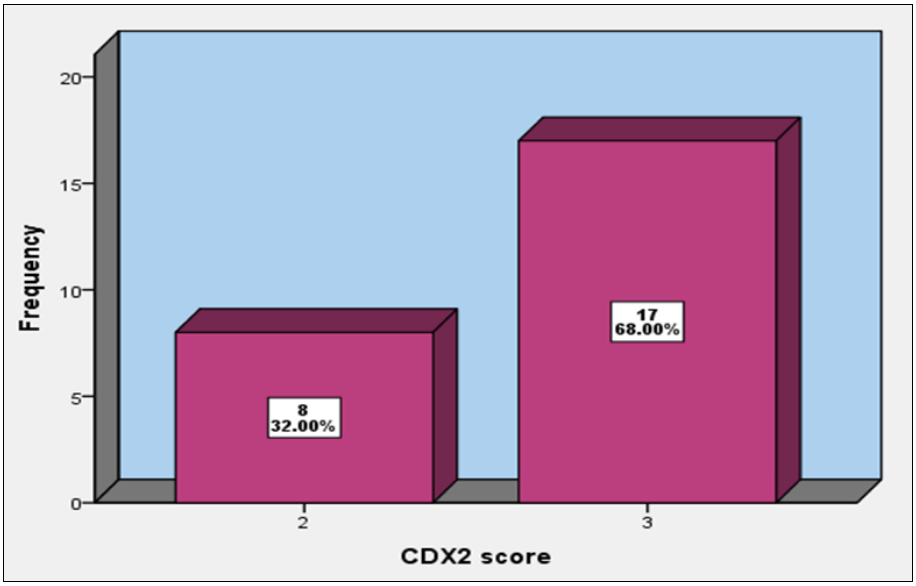


**Fig 1:** Distribution of patients according to CDX2 score.

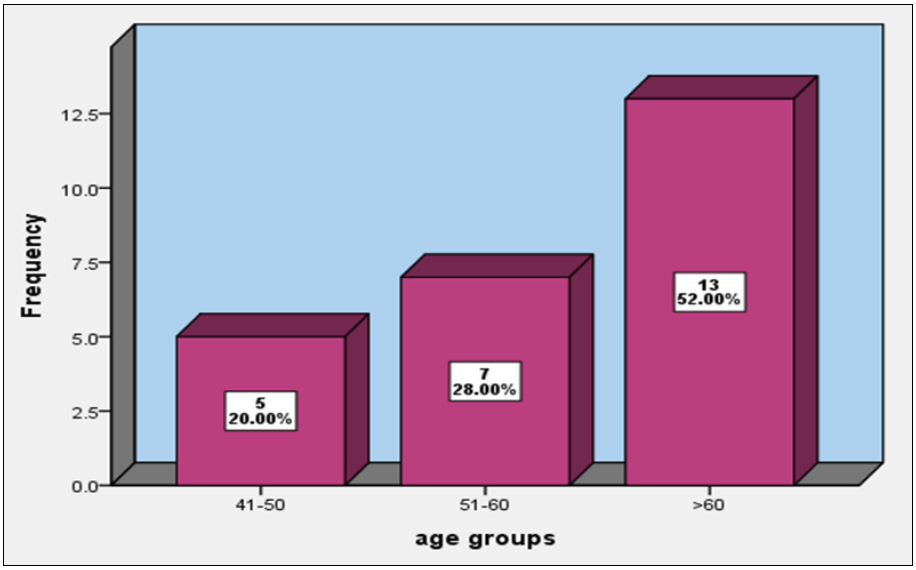


**Fig 2:** Distribution of patients according to age groups.

There is no significant association between CDX2 score and (stage, age group, gender, L.N. involvement and grade). As show in table 2.

**Table 2:** Association between CDX2 score and variables in current study.

| Variables | | CDX2 score | | P-value |
|---|---|---|---|---|
| | | **2** | **3** | |
| Stage | 2 | 2 | 3 | 0.57 |
| | | 25.0% | 17.6% | |
| | 3 | 6 | 12 | |
| | | 75.0% | 70.6% | |
| | 4 | 0 | 2 | |
| | | 0.0% | 11.8% | |
| | Total | 8 | 17 | |
| | | 100.0% | 100.0% | |
| Age group | 41-50 | 3 | 2 | |
| | | 37.5% | 11.8% | |
| | 51-60 | 3 | 4 | 0.147 |
| | | 37.5% | 23.5% | |
| | >60 | 2 | 11 | |
| | | 25.0% | 64.7% | |
| | Total | 8 | 17 | |
| | | 100.0% | 100.0% | |
| Gender | Female | 4 | 6 | |

| | | | | |
|---|---|---|---|---|
| | | 50.0% | 35.3% | |
| | Male | 4 | 11 | |
| | | 50.0% | 64.7% | |
| | Total | 8 | 17 | 0.39 |
| | 0 | 100.0% | 100.0% | |
| | | 5 | 11 | |
| L.N. | 1 | 62.5% | 64.7% | |
| | | 2 | 2 | |
| | 2 | 25.0% | 11.8% | |
| | | 1 | 4 | |
| | Total | 12.5% | 23.5% | |
| | | 8 | 17 | 0.63 |
| Grade | 1 | 100.0% | 100.0% | |
| | | 0 | 1 | |
| | 2 | 0.0% | 5.9% | |
| | | 7 | 16 | |
| | 3 | 87.5% | 94.1% | |
| | | 1 | 0 | |
| | Total | 12.5% | 0.0% | 0.27 |
| | | 8 | 17 | |
| | | 100.0% | 100.0% | |

P-value ≤ 0.05 (significant).

There is no significant difference between mean of tumor size according to CDX2 score (2, 3). As show in table 3 and fig 3.

**Table 3:** Difference between mean of tumor size according to CDX2 score (2, 3).

| CDX2 score | N | Mean | SD | Min | Max | P-value |
|---|---|---|---|---|---|---|
| 2 | 8 | 4.938 | 1.7816 | 2.0 | 7.0 | 0.556 |
| 3 | 17 | 5.600 | 2.8747 | 2.2 | 14.0 | |

P-value ≤ 0.05 (significant).

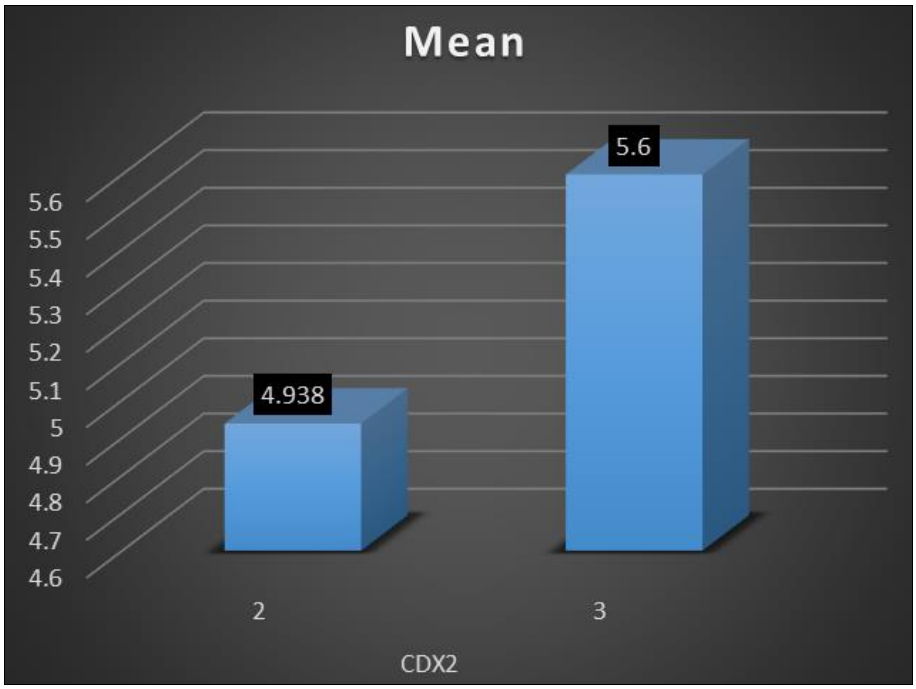


**Fig 3:** No significant difference between mean of tumor size according to CDX2 score (2, 3).

**B. Gastric carcinoma**

25 Patients with colorectal Ca., mean age of patients (50.6 ± 13) years old. With Min (24) and Max. (69) years old. Mean size of tumor (5.94 ± 2.94) mm. 17 (68%) of patients are males and 8 (32%) are females, 20 (80%) of patients are at stage 3 of illness, 14 (56%) of patients are at grade 2 of illness, 7 (28%) of patients 0, 1 involvement of lymph node. As show in table 4.

**Table 4:** Distribution of variables in current study.

| Variables | | frequency | percentage |
|---|---|---|---|
| Gender | Female | 8 | 32.0 |
| | Male | 17 | 68.0 |

| | | | |
|---|---|---|---|
| Stage | *2* | 2 | 8.0 |
| | *3* | 20 | 80.0 |
| | *4* | 3 | 12.0 |
| Grade | *1* | 2 | 8.0 |
| | *2* | 14 | 56.0 |
| | *3* | 9 | 36.0 |
| Lymph node | *0* | 7 | 28.0 |
| | *1* | 7 | 28.0 |
| | *2* | 5 | 20.0 |
| | *3* | 6 | 24.0 |

According to fig (4, 5); 10 (40%) of patients have CDX2 score (0), 9 (36%) of them have CDX2 score (1). 8 (32%) of patients at age group 41-50 years while 7 (28%) of patients at age group >60 years.

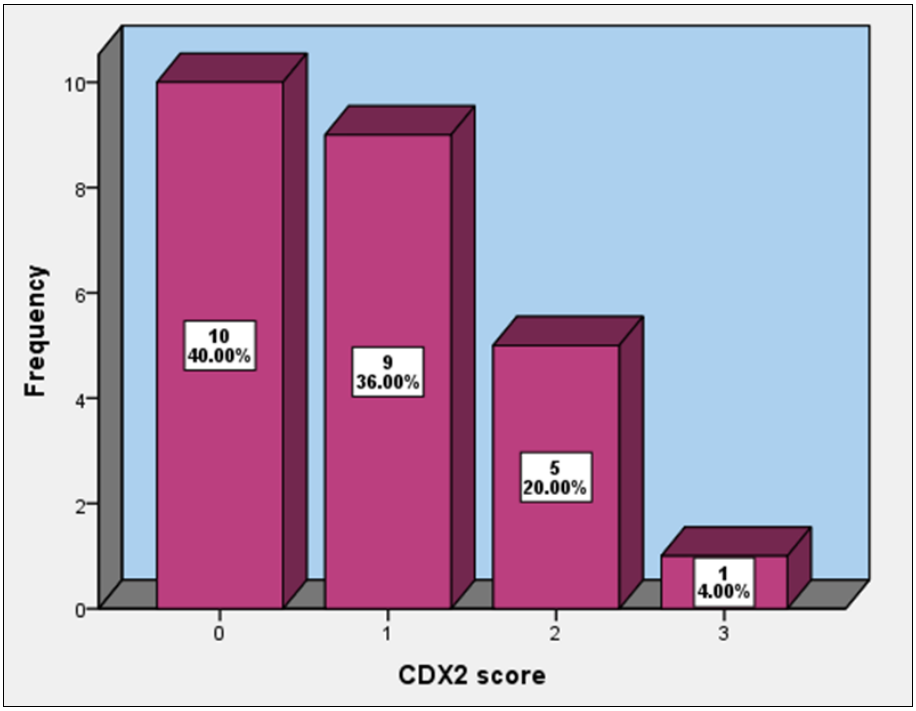


**Fig 4:** Distribution of patients according to CDX2 score.

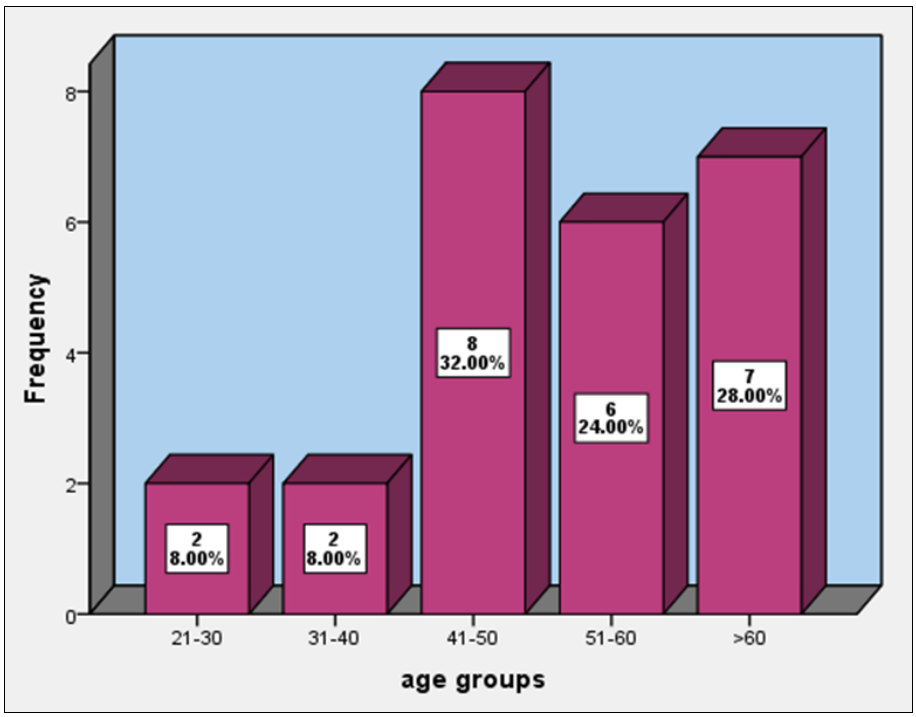


**Fig 5:** Distribution of patients according to age groups.

There is no significant association between CDX2 score and (stage, age group, gender, L.N. involvement and grade). As show in table 5.

**Table 5:** Association between CDX2 score and variables in current study.

| Variables | | CDX2 score | | | | P-value |
|---|---|---|---|---|---|---|
| | | **0** | **1** | **2** | **3** | |
| Stage | 2 | 2 | 0 | 0 | 0 | 0.72 |
| | | 20.0% | 0.0% | 0.0% | 0.0% | |
| | 3 | 7 | 8 | 4 | 1 | |
| | | 70.0% | 88.9% | 80.0% | 100.0% | |
| | 4 | 1 | 1 | 1 | 0 | |
| | | 10.0% | 11.1% | 20.0% | 0.0% | |
| | total | 10 | 9 | 5 | 1 | |
| | | 100.0% | 100.0% | 100.0% | 100.0% | |
| Age group | 21-30 | 1 | 1 | 0 | 0 | 0.79 |
| | | 10.0% | 11.1% | 0.0% | 0.0% | |
| | 31-40 | 1 | 1 | 0 | 0 | |
| | | 10.0% | 11.1% | 0.0% | 0.0% | |
| | 41-50 | 4 | 3 | 0 | 1 | |
| | | 40.0% | 33.3% | 0.0% | 100.0% | |
| | 51-60 | 2 | 2 | 2 | 0 | |
| | | 20.0% | 22.2% | 40.0% | 0.0% | |
| | >60 | 2 | 2 | 3 | 0 | |
| | | 20.0% | 22.2% | 60.0% | 0.0% | |
| | total | 10 | 9 | 5 | 1 | |
| | | 100.0% | 100.0% | 100.0% | 100.0% | |
| Gender | female | 3 | 4 | 0 | 1 | 0.16 |
| | | 30.0% | 44.4% | 0.0% | 100.0% | |
| | male | 7 | 5 | 5 | 0 | |
| | | 70.0% | 55.6% | 100.0% | 0.0% | |
| | total | 10 | 9 | 5 | 1 | |
| | | 100.0% | 100.0% | 100.0% | 100.0% | |
| L.N. | 0 | 4 | 1 | 2 | 0 | 0.4 |
| | | 40.0% | 11.1% | 40.0% | 0.0% | |
| | 1 | 4 | 2 | 1 | 0 | |
| | | 40.0% | 22.2% | 20.0% | 0.0% | |
| | 2 | 1 | 2 | 1 | 1 | |
| | | 10.0% | 22.2% | 20.0% | 100.0% | |
| | 3 | 1 | 4 | 1 | 0 | |
| | | 10.0% | 44.4% | 20.0% | 0.0% | |
| | Total | 10 | 9 | 5 | 1 | |
| | | 100.0% | 100.0% | 100.0% | 100.0% | |
| Grade | 1 | 1 | 0 | 1 | 0 | 0.31 |
| | | 10.0% | 0.0% | 20.0% | 0.0% | |
| | 2 | 7 | 3 | 3 | 1 | |
| | | 70.0% | 33.3% | 60.0% | 100.0% | |
| | 3 | 2 | 6 | 1 | 0 | |
| | | 20.0% | 66.7% | 20.0% | 0.0% | |
| | Total | 10 | 9 | 5 | 1 | |
| | | 100.0% | 100.0% | 100.0% | 100.0% | |

P-value ≤ 0.05 (significant).

There is no significant difference between mean of tumor size according to CDX2 score (0, 1, 2, 3). As show in table 6 and fig 6.

**Table 6:** Difference between mean of tumor size according to CDX2 score.

| CDX2 score | N | Mean | SD | Min | Max | P-value |
|---|---|---|---|---|---|---|
| 0 | 10 | 5.8 | 2.7 | 1.0 | 10.0 | 0.556 |
| 1 | 9 | 5.8 | 3.1 | 2.5 | 13.0 | |
| 2 | 5 | 6.7 | 3.6 | 2.5 | 11.0 | |
| 3 | 1 | 4 | . | 4.0 | 4.0 | |

P-value ≤ 0.05 (significant).

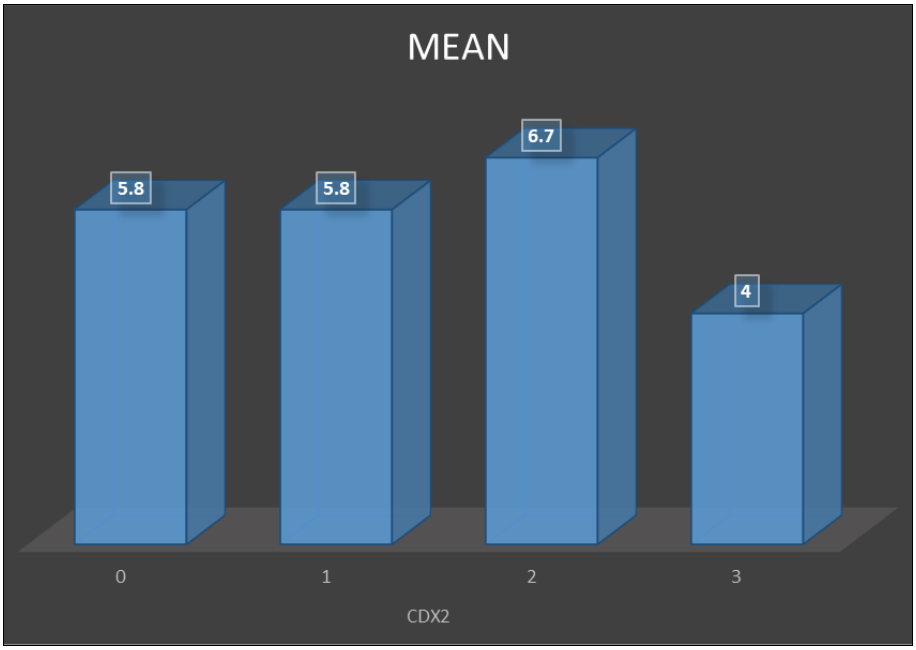


**Fig 6:** No significant difference between mean of tumor size according to CDX2 score (0, 1, 2, 3).

According to table 7, there is significant association between CDX2 score and site of cancer. 10 (40%) of patients with gastric Ca. have CDX2 score (0), 9 (36%) of patients with gastric Ca. have CDX2 score (1), while 8 (32%) of patients with colorectal Ca. have CDX2 score (2), 17 (68%) of patients with colorectal Ca. have CDX2 score (3).

**Table 7:** Association between CDX2 score and site of cancer.

| Variables | | Site | | p-value |
|---|---|---|---|---|
| | | colorectal | gastric | |
| CDX2 score | 0 | 0 | 10 | |
| | | 0.0% | 40.0% | |
| | 1 | 0 | 9 | |
| | | 0.0% | 36.0% | 0.0001 |
| | 2 | 8 | 5 | |
| | | 32.0% | 20.0% | |
| | 3 | 17 | 1 | |
| | | 68.0% | 4.0% | |
| Total | | 25 | 25 | |
| | | 100.0% | 100.0% | |

p-value ≤ 0.05 (significant).

## Discussion

CDX2 is a caudal-homeobox gene that encodes for a transcription factor that is important in the proliferation and differentiation of epithelial cells in the intestine. It is expressed by majority of colorectal carcinomas, and some cases of primary mucin-producing carcinomas of ovary, bladder, lung and pancreaticobiliary adenocarcinomas [12]. In the current study, a semiquantitative method has been used to calculate the expression of CDX2 by using the percentage of intensely stained nuclei and the as mentioned previously at the material and method chapter, while other studies used different scoring method as Lopes, N., Bergsland, C.H., Bjørnslett, M. *et al.* in 2020 [13] who estimated proportion of positive cells (score value ranging from 0 to 5; 0 = none, 1 ≤ 1%, 2 = 1–10%, 3 = 11–33%, 4 = 34–66%, and 5 = 67–100%) Masood MA *et al.* in 2016 [14] interpreted as either positive or negative Gastric carcinomas were considered CDX2 positive when nuclear expression of CDX2 immuno-histochemical stain was seen in tumor cells. Regarding clinicopathological parameters, 25 cases were taken most cases in this study were males (68% of cases), with highest incidence (32% of cases) among age group 41-50 years and TNM stage T3 (80% of cases),most of the cases (56%) were moderately differentiated adenocarcinoma (G2), which agree with Masood MA *et al.* in 2016 [14] who found that The mean age of included patients was 50y, with preponderance of males at 60.4%, and 66.3% had tumor stage T3. Regarding the expression of Cdx2 in gastric adenocarcinoma in this study we found that (40%) of patients have CDX2 score (0), (36%) have CDX2 score (1), 20% of patients have score (2), 4% have score (3), this is in contrast to Masood MA *et al.* in 2016 [14] who found that 30.7% of these were CDX2 positive while the remaining 69.3% were CDX2 negative this may be due to larger sample size and different scoring technique. In a study by Fan Z. *et al.* in 2005 [15] Cdx2 was expressed in the nuclei of gastric carcinoma cells in 36.7% (40 of 109) of cases, while in this study it was expressed in 60% (15 of 25) of cases. In this study there was no significant association between CDX2 score and (stage, age group, gender, L.N. involvement and grade), this is in contrast to Camilo *et al.* in 2014 [16] who found that strong expression of CDX2 was significantly associated with lower TNM stage in a series of 201 cases. Regarding clinicopathological parameters, 25 cases were taken most of them were males (60% of cases), with highest incidence (52% of cases) among age group >

60 years, stage T3 (72% of cases) and moderately differentiated G2 (92% of cases) which agree with Sen A, Mitra S *et al*. in 2015 [17] who found that Moderately differentiated adenocarcinoma was the most common histopathological type responsible for 69.1% of cases, the most common TNM stage was $T_3$ (39.7%). Regarding expression of CDX2, we found that all the 25 cases expressed it with 32% of the patients have score (2) while the remainder 68% have score (3), this agree with Saad *et al.* in 2014 [10]. CDX2 was found to be expressed in 29 of 30 metastatic colorectal adenocarcinomas but he also found that The majority of the cases (21/30 [70%]) demonstrated strong (3+) and diffuse immunostaining in more than 75% of the cells, 5 cases showed strong staining (3+) of 51% to 75% of the cells; and 3 cases showed moderate staining (2+) of 26% to 50% of the cells; this controversy is may be due to different scoring method in both studies Kaimaktchiev *et al*. in 2004 [18]. examined CDX2 expression in a series of tissue microarrays with normal and neoplastic tissues. Strong nuclear staining for CDX2 was observed in 86% of colonic adenocarcinomas, decreased CDX2 staining correlated with increased tumor stage. Regarding relation between the score of CDX2 expression and clinicopathological data (TNM stage, grade of differentiation, age group, gender and L.N involvement), reflecting the findings of Sen A, Mitra S *et al*. in 2015 [17] who found that there was no significant difference in the staining of well and moderately differentiated tumor, TNM stage and tumor size. This study also concurred with Saad *et al*. in 2004 who also suggested that CDX2 should not be used as the sole basis for determining whether the gastrointestinal tract is the primary site of adenocarcinoma and be used as a part of a broader immunohistochemical panel (10) such as CK7, CK20, The CK7–/CK20+ immunophenotype was expressed by 22 (73%) of 30 metastatic colorectal carcinomas, unfortunately this study did not include metastatic cases.

## Conclusion

CDX2 marker is already proven as highly sensitive in colorectal adenocarcinoma. There was a significant correlation between CDX2 score and the site of the tumor (colorectal versus gastric).

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